

Review

Genomic Imprinting: Implications for Human Disease

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Genomic imprinting refers to an epigenetic marking of genes that results in monoallelic expression. This parent-of-origin dependent phenomenon is a notable exception to the laws of Mendelian genetics. Imprinted genes are intricately involved in fetal and behavioral development. Consequently, abnormal expression of these genes results in numerous human genetic disorders including carcinogenesis. This paper reviews genomic imprinting and its role in human disease. Additional information about imprinted genes can be found on the Genomic Imprinting Website at <http://www.geneimprint.com>. (*Am J Pathol* 1999, 154:635–647)

Genomic imprinting (also referred to as gametic or parental imprinting) is the epigenetic marking of a gene based on its parental origin that results in monoallelic expression. Genomic imprinting differs from classical genetics in the sense that the parental complement of imprinted genes are not equivalent with respect to their expression, despite both parents contributing equally to the genetic content of their progeny. The mechanism of imprinting is complex and not completely understood; however, evidence suggests that the “imprint mark” is a parental-specific methylation of CpG-rich domains that is established during gametogenesis. The imprint marks on a gene must be erasable in the germline when transmitted through individuals of the opposite sex, but maintained during somatic cell division (Figure 1).

The total number of publications on genomic imprinting has increased markedly over the past 10 years and has now reached almost 1500 (Figure 2). There are now more than 25 identified imprinted genes (Table 1), and estimates based on mouse models indicate that as many as 100 to 200 may exist.¹ Imprinted genes are involved in many aspects of development including fetal and placental growth, cell proliferation, and adult behavior. Conse-

quently, alteration of normal imprinting patterns gives rise to numerous human genetic diseases including cancer. This review examines the role of genomic imprinting in several human genetic diseases such as the Beckwith-Wiedemann, Prader-Willi, and Angelman syndromes, as well as the evidence implicating genomic imprinting in behavioral disorders and carcinogenesis. For excellent reviews on the mechanistic models of genomic imprinting, consult Reik and Walter,² Constancia et al³, and Barlow.⁴

Background

Genomic imprinting plays a critical role in embryogenesis as evidenced by certain aberrations of human pregnancy. The complete hydatidiform mole arises from the fertilization of an anuclear egg either by a haploid sperm (followed by duplication of the paternal genome) or two haploid sperm (diandric diploidy).⁵ This trophoblastic disease is characterized by a completely androgenetic (Ag) genome and results in reduced or absent fetal growth coupled with hyperplastic extraembryonic growth.^{6,7} In contrast, ovarian dermoid cysts arise from the spontaneous activation of an ovarian oocyte resulting in the duplication of the maternal genome.⁸ These abnormalities indicate that normal human development proceeds only when a complete complement of the paternal and maternal genomes is present.

Experimental evidence for the requirement of both the maternal and paternal chromosomal complements was demonstrated through the manipulation of mouse embryos.^{9,10} Mouse embryos were altered *in vitro* to produce diploid Ag or diploid parthenogenetic (Pg) embryos, possessing only paternal or maternal chromosomes, respectively. Similarities to the human pregnancy aberrations were apparent since Ag mouse embryos had reduced fetal growth and proliferative extraembryonic growth while Pg embryos maintained relatively normal fetal growth but exhibited poor extraembryonic growth. Nei-

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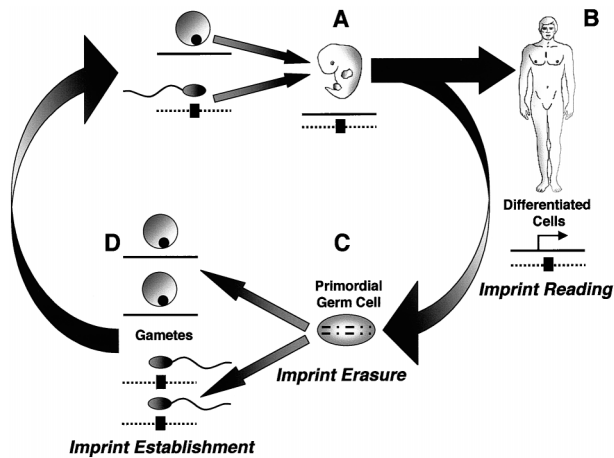


Figure 1. Imprint establishment and propagation during gametogenesis and development. The paternal allele (dashed line) is imprinted and the maternal allele is expressed (solid line). The "imprint mark" (black box) represents a parental-specific methylation established during gametogenesis. A: The maternal and paternal genomes have different imprint patterns following fertilization. B: Both "imprint marks" and imprint reading are maintained during somatic cell division. C: The parental specific imprints are erased in the primordial germ cells. D: The appropriate "imprint marks" are reestablished for the next generation.

ther Ag nor Pg embryos were viable to term.^{9,10} This demonstrates that genes expressed exclusively from one parental genome exist, and abnormal embryonic development results from the loss of function of these mono-allelically expressed genes. A mark or imprint conferring parental memory must therefore differentiate between the parental genomes, be present on the parental chromosomes through cell division, and be inheritable. This was confirmed when nuclei from early haploid preimplantation embryos were transplanted into fertilized eggs following the removal of one pronucleus. The embryo was viable only if the sex of the donor nucleus was opposite that of the remaining pronucleus.¹¹

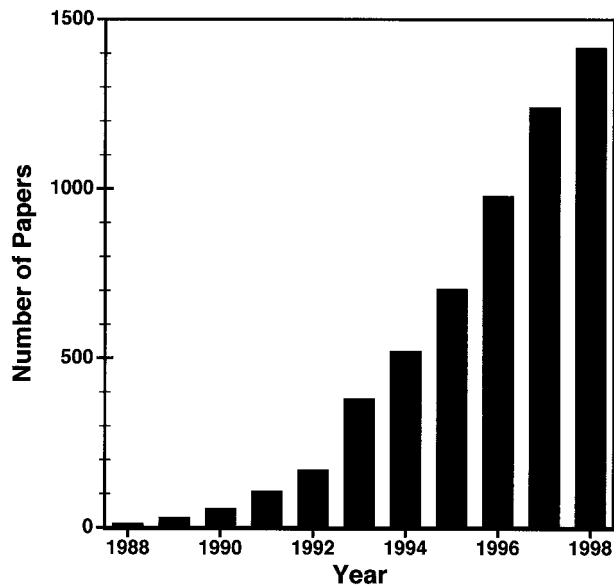


Figure 2. Total number of papers published on genomic imprinting versus time.

The chromosomal regions responsible for the genomic imprinting effects observed in mouse embryos were mapped to specific mouse chromosomes by artificially generating uniparental disomies (UPD) in mice. Certain regions of distinct chromosomes were responsible for markedly different phenotypes ranging from embryonic lethality to various growth and developmental defects apparent only after birth. These effects were dependent on whether the two copies were inherited entirely from one parent, resulting in either duplication or deficiency of genes in these chromosomal regions.¹²⁻¹⁴ It was initially postulated that only mouse chromosomes 2, 6, 7, 11, 12, and 17 harbored imprinted chromosomal regions.¹⁵ However, there are now reports of other chromosomes either containing more localized areas of genomic imprinting or harboring genes that show more subtle imprinted effects.

UPD also results in phenotypic abnormalities in humans. These include maternal UPD for chromosomes 2, 7, 14, 15, and 16, and paternal UPD for chromosomes 6, 11, 14, 15, and 20.¹⁶ Classic examples of diseases associated with regional maternal and paternal UPD on chromosome 15 include the Prader-Willi syndrome and Angelman syndrome, respectively. Investigations of these genetic diseases are now helping to elucidate the mechanisms of genomic imprinting in humans.

Imprinting of Specific Genes

The first endogenous imprinted gene identified was mouse insulin-like growth factor 2 (*Igf2*), which encodes for a critical fetal-specific growth factor. A targeted mutation in *Igf2* gave rise to a heterozygous dwarfing phenotype when the mutation was passed from the father while the offspring were normal when the mutation was inherited from the mother.¹⁷ Furthermore, the dwarfing phenotype was observed in paternal heterozygotes and homozygotes suggesting that *Igf2* gene expression is exclusively from the paternal allele. At about the same time, the mannose 6-phosphate/insulin-like growth factor type 2 receptor (*M6p/Igf2r*) gene was shown to be imprinted and maternally expressed in mice.¹⁸ Interestingly, the products of these oppositely imprinted genes interact at the biochemical level since the degradation of *Igf2* occurs via the *M6p/Igf2r*.¹⁹ When a mutation was targeted to the *M6p/Igf2r* in mice, maternal heterozygotes or homozygotes showed a 30% increase in fetal growth, but they were not viable at birth.²⁰ Thus, the reciprocally imprinted *Igf2* and *M6p/Igf2r* genes both play an important role in regulating embryonic development and fetal growth.^{17,20}

Numerous techniques have now been used to identify additional imprinted genes. Positional cloning coupled with candidate gene testing has identified novel human imprinted genes located in imprinted clusters at chromosome positions 11p15.5 and 15q11-q13. Techniques have also used parental differences in DNA methylation and expression to identify imprinted genes. Subtractive hybridization or differential display using cDNA from Pg, Ag, and fertilized embryos have yielded novel imprinted

Table 1. Identified Imprinted Genes and Transcripts

Human			Mouse			References
Gene	Location	Expressed allele	Gene	Location	Expressed allele	
<i>NOEY2 (ARHI)</i>	1p31	Paternal				129
<i>p73</i>	1p36	Maternal				147, 148
<i>U2AFBPL</i>	5q22-q31	Biallelic	<i>U2afbp-rs</i>	Proximal 11	Paternal	25, 149, 150
<i>MAS1</i>	6q25.3-q26	Biallelic/ Monoallelic in breast	<i>Mas</i>	Proximal 17	Paternal	151–153
<i>M6P/IGF2R</i>	6q26-q27	Biallelic/ Maternal*	<i>M6p/Igf2r</i>	Proximal 17	Maternal	18, 136–139
<i>GRB10</i>	7p11.2-12	NR	<i>Igf2r-AS</i>	Proximal 17	Paternal	4, 140
<i>PEG1/MEST</i>	7q32	Paternal	<i>Meg1/Grb10</i>	Proximal 11	Maternal	31
<i>WT1</i>	11p13	Biallelic/ Maternal*	<i>Peg1/Mest</i>	Proximal 6	Paternal	21, 154, 155
<i>ASCL2/HASH2</i>	11p15.5	Maternal	<i>Wt1</i>	2	NR	120, 156
<i>H19</i>	11p15.5	Maternal	<i>Mash2</i>	Distal 7	Maternal	157, 158
<i>IGF2</i>	11p15.5	Paternal	<i>H19</i>	Distal 7	Maternal	30, 159
<i>IMPT1/BWR1A/ ORCTL2/TSSC5</i>	11p15.5	Maternal	<i>Igf2</i>	Distal 7	Paternal	17, 36, 160–162
<i>INS</i>	11p15.5	Biallelic	<i>Igf2-AS</i>	Distal 7	Paternal	36
<i>IPL/TSSC3/BWR1C</i>	11p15.5	Maternal	<i>Impt1</i>	Distal 7	Maternal	163–166
<i>ITM</i>	11p15.5	NR	<i>Ins2</i>	Distal 7	Paternal	167–169
<i>KvLQT1</i>	11p15.5	Maternal	<i>Ipl</i>	Distal 7	Maternal	164, 170, 171
<i>p57^{KIP2}/CDKN1C</i>	11p15.5	Maternal	<i>Itm</i>	Distal 7	Maternal	172
<i>TAPA1</i>	11p15.5	Biallelic†	<i>Kvlqt1</i>	Distal 7	Maternal	62, 173
<i>HTR2A</i>	13q14	Biallelic/ Maternal*	<i>p57^{KIP2}</i>	Distal 7	Maternal	48, 122, 174
<i>FNZ127</i>	15q11-q13	Paternal	<i>Tapa1</i>	Distal 7	Maternal?	27, 67, 104
<i>GABRA5</i>	15q11-q13	Paternal?†	<i>Htr2</i>	14,Band D3	Maternal	145, 175, 176
<i>GABRB3</i>	15q11-q13	Paternal?†				177
<i>GABRG3</i>	15q11-q13	Paternal?†	<i>Gabra5</i>	Central 7	Biallelic	26, 27, 178
<i>IPW</i>	15q11-q13	Paternal	<i>Gabrb3</i>	Central 7	Biallelic	26, 27, 179
<i>NDN (necdin)</i>	15q11-q13	Paternal	<i>Gabrg3</i>	Central 7	Biallelic	26, 27, 178
<i>PAR1</i>	15q11-q13	Paternal	<i>Ipw</i>	Central 7	Paternal	35, 177, 180, 181
<i>PAR5</i>	15q11-q13	Paternal	<i>Ndn</i>	Central 7	Paternal	82, 181, 182
<i>PAR-SN</i>	15q11-q13	Paternal				177, 180
<i>SNRPN</i>	15q11-q13	Paternal	<i>Snrpn</i>	Central 7	Paternal	177, 180
<i>UBE3A</i>	15q11-q13	Maternal	<i>Ube3a</i>	Central 7	Maternal	183
<i>ZNF127</i>	15q11-q13	Paternal	<i>Zfp127</i>	Central 7	Paternal	84, 184–186
<i>PEG3</i>	19q13.4	Paternal	<i>Peg3/Apoc2</i>	Proximal 7	Paternal	77–79
<i>Neuronatin</i>	20q11.2-q12	NR	<i>Peg5/Nnat</i>	Distal 2	Paternal	80, 181, 187
<i>GNAS1</i>	20q13	Paternal	<i>Gnas1</i>	Distal 2	Maternal/ Paternal	22, 188
<i>XIST</i>	Xq13.2 (XIC)‡	Paternal?	<i>Xist</i>	Xic	Paternal	23, 189, 190
			<i>Grf1/Cdc25^{Mm}</i>	Distal 9	Paternal	191–194
			<i>Impact</i>	Proximal 18	Paternal	195–200
			<i>Ins1</i>	Distal 19	Paternal	24
						201
						167, 202

NR, not reported.
 * Polymorphic imprinting.
 † Determined *in vitro*.
 ‡ X-inactivation center.

genes such as *Peg1/Mest*, a mesoderm restricted hydrolyase at mouse chromosome 6; *Peg3*, a novel zinc-finger protein on proximal mouse chromosome 7; and *Peg5/Nnat* located on mouse chromosome 2.^{21–23} The *Grf1* and *U2af1-rs1* imprinted genes were identified by a genome-wide screen termed restriction landmark genome screening (RLGS).^{24,25} Finally, three GABAA receptor subunit genes (*GABRB3*, *GABRA5*, and *GABRG3*) were shown to be exclusively expressed from the paternal allele by microcell-mediated chromosome transfer.²⁶ More recently,

results from a somatic-cell hybrid system indicated that these receptor subunit genes were not imprinted.²⁷

Characteristics of Imprinted Genes

Several theories have been proposed for the endogenous function of genomic imprinting. Moore and Haig²⁸ have suggested that genomic imprinting in mammals has evolved from a conflict of interest between the paternal and maternal genome in regulating fetal growth. Whereas

benefits of a large placenta and fetus might ensure future propagation of a paternal line, the result may tax the resources of the mother, thereby compromising future pregnancies. Conversely, if fetal and placental growth is held in check, more offspring from the mother's (and possibly different father's) lineage may be produced. Accordingly, the mother would be predicted to imprint or silence genes that promote placental and fetal growth, whereas the father would imprint genes that inhibit growth.

In support of this theory, the gene encoding the fetal growth factor, *Igf2*, is maternally imprinted, whereas *H19*, which encodes for an untranslated RNA involved in silencing *Igf2* expression, is paternally imprinted.^{17,29,30} The result of this reciprocal imprinting is parent-of-origin, monoallelic paternal expression of the gene encoding for *Igf2*. Interestingly, the genes that encode for the M6p/*Igf2r* which degrades *Igf2*, and *Meg1/Grb10* which inhibits *Igf2* signaling are both paternally imprinted, adding further support for this theory.^{18,19,31}

An alternative proposal for imprinting suggests that the cytosine methylation involved in imprint regulation evolved as a defense mechanism for the inactivation of parasitic sequences such as transposable elements and proviral DNA.³² This is supported by the finding that 5-aza-deoxycytidine, an inhibitor of cytosine DNA methyltransferase, activates silent retroviruses.³³ Irrespective of the reason for the evolution of genomic imprinting in mammals, the functional consequences of genomic imprinting include the inhibition of parthenogenesis and the loss of protection from deleterious recessive mutations.

As more imprinted genes are identified, the characteristics of imprinting are becoming apparent. For example, two chromosomal regions harbor more than one imprinted gene. These imprinting clusters reside at human chromosome 11p15.5 (syntenic to the distal region of mouse chromosome 7) and human chromosome 15q11-q13 (syntenic to the central region of mouse chromosome 7). Within these imprinted gene clusters, genes have been identified that encode for untranslated RNA^{34,35} and antisense RNA^{36,37} that may be involved in imprint control. Some imprinted genes, such as *H19* and *IGF2*, that are located in imprinted clusters show coordinate regulation. Imprinted genes also often reside in chromosomal regions that undergo asynchronous replication,^{38,39} and the meiotic recombination frequencies in these regions may differ between the male and female germ cells.⁴⁰ Another characteristic of imprinted genes is an associated allele-specific DNA methylation of cytosine residues in CpG dinucleotides that appears to distinguish the parental alleles.⁴¹⁻⁴³ Repetitive elements associated with the areas of differential methylation have also been identified in several imprinted genes (ie, *H19*, *M6p/Igf2r*, *U2afbp-rs*, and *p57^{KIP2}*).⁴⁴⁻⁴⁸

Imprinting in Genetic Diseases

Beckwith-Wiedemann Syndrome

There are a number of human genetic diseases associated with imprinting defects (reviewed in Refs. 49 and

50). Beckwith-Wiedemann syndrome (BWS) maps to 11p15 and is characterized by general overgrowth with symptoms including hemihypertrophy, macroglossia, and visceromegaly. Genomic imprinting in BWS was first suspected when preferential maternal transmission of mutations was observed in some BWS families.⁵¹ Additionally, approximately 10-20% of BWS individuals are predisposed to embryonal tumors, the most frequent of which are Wilms' tumors and adrenocortical carcinoma.⁵² The rate of Wilms' tumor formation in the BWS population is 1000-fold higher than in the normal population, and these tumors often show preferential loss of maternal 11p15.⁵³ The majority of BWS cases arise sporadically; however, in both sporadic and familial forms, a small percentage exhibits UPD at chromosome 11p15. In these cases, the remainder of the chromosome is biparental in inheritance, indicative of somatic mosaicism through a postfertilization mitotic recombination event.^{54,55}

The most common molecular event occurring in BWS patients that do not have cytogenetic abnormalities is the biallelic expression of *IGF2* due to loss of imprinting (LOI).^{56,57} LOI at the *IGF2* locus may be accompanied by the methylation and/or silencing of the active maternal allele of *H19*.^{58,59} This *H19*-dependent event is consistent with an enhancer-competition model for the co-regulation of these genes.⁶⁰

Translocations in BWS patients may also lead to LOI at the *IGF2* locus, but without loss of *H19* imprinting.⁶¹ These translocations affect imprinting by disrupting a gene involved in imprint control, or by altering the function of an imprinting center (IC). Therefore, disruption of *IGF2* imprinting in BWS may also occur via an *H19*-independent event.^{56,57} The imprinted *KvLQT1* gene located centromeric to *IGF2* spans a common breakpoint region in BWS, and has been proposed to maintain regional imprint control at 11p15.5.⁶⁰ *KvLQT1* shows preferential expression from the maternal allele in most tissues examined except the heart where it is biallelically expressed.⁶² This explains why *KvLQT1*, responsible for the autosomal dominant cardiac arrhythmia long QT syndrome, shows no parent-of-origin effect in this disorder. The maternally expressed *p57^{KIP2}*, which encodes for a cyclin-dependent kinase inhibitor, also maps to 11p15.5. Abnormal imprinting and epigenetic silencing of *p57^{KIP2}* is found in some individuals with BWS,⁶³ and mutations are present in about 5% of BWS patients.⁶⁴⁻⁶⁶

To date, ten imprinted genes have been mapped to 11p15.5 (Table 1). Flanking these imprinted genes are the non-imprinted *NAP2* (centromeric border) and *L23MRP* (telomeric border) genes.⁶⁷ The syntenic region in the mouse, distal chromosome 7, confirms the existence of an imprinting cluster at this chromosomal location.⁶⁸ A possible explanation for the involvement of multiple genes in BWS (even if *IGF2* overexpression is directly responsible for BWS) is that one or more of the adjacent genes (eg, *H19*, *p57^{KIP2}*, *KvLQT1*) are involved in the regulation of *IGF2* expression. Experimental evidence supports this postulate since transgenic mice that overexpress *Igf2* develop symptoms similar to BWS.⁶⁹

Prader-Willi and Angelman Syndromes

Two clinically distinct genetic diseases associated with genomic imprinting on chromosome 15q11-q13 are the Prader-Willi syndrome (PWS) and the Angelman syndrome (AS). Each syndrome is associated with deficiencies in sexual development and growth, and behavioral and mental problems including retardation.^{70,71} Major diagnostic criteria for PWS patients include hypotonia, hyperphagia and obesity, hypogonadism and developmental delay.⁷² AS patients often display ataxia, tremulousness, sleep disorders, seizures, and hyperactivity. Severe mental retardation accompanied with a lack of speech may also be present, but AS individuals often display a happy disposition with outbreaks of laughter.⁷³

PWS and AS are autosomal dominant disorders showing parent-of-origin effects since the inherited diseases are transmitted from only one of the parents. Approximately 70% of PWS and AS individuals have a *de novo* 3- to 4-megabase deletion in their paternal or maternal chromosome 15q11-q13, respectively. Maternal UPD occurs in most of the remaining PWS patients (25%); however, paternal UPD only occurs in about 4% of AS patients.^{16,74} The preferential loss of parental alleles associated with different phenotypes, coupled with the instances of UPD indicate the involvement of imprinted genes (ie, paternally expressed gene(s) for PWS and maternally expressed gene(s) for AS).⁷⁰ Recently, approximately 20% of the AS patients without a chromosomal deletion were found to have truncating mutations in *UBE3A*, a gene encoding a ubiquitin protein ligase involved in protein turnover.^{75,76} *UBE3A*, mapped to 15q11-q13, has now been reported to be maternally expressed in the human brain.^{77,78} Thus, abnormalities in the maternal-specific expression of *UBE3A* during brain development has been proposed for AS.⁷⁹ This region also harbors four imprinted, paternally expressed candidate PWS genes: small nuclear riboprotein-associated polypeptide N (*SNRPN*), Imprinted in Prader-Willi (*IPW*), zinc finger 127 (*ZNF127*), and necdin (*NDN*).^{35,80-82} The imprinted, paternally expressed transcripts of *PAR1*, *PAR5*, and *PAR-SN* may also be involved in PWS.

Imprinting defects resulting from microdeletions targeted to the *SNRPN* gene have been identified in a small percentage of PWS patients that maintain both parental complements of 15q11-q13.^{80,83,84} These deletions alter *SNRPN* promoter methylation and prevent expression of its paternal allele. This results in the silencing of other paternally expressed genes in the cluster.^{83,85} These microdeletions apparently disrupt an imprinting center⁸⁵ involved in resetting the correct imprinting pattern during gametogenesis.^{84,85} The alternate use of *SNRPN* transcripts (BD exons) may be involved in the normal imprinting process.⁸⁶ Offspring inheriting microdeletions from their mother exhibit no apparent phenotype; however, a subsequent paternal transmission results in PWS. In comparison, a small percentage of AS patients have similar microdeletions in the *SNRPN* gene (albeit in a region farther upstream) that disrupt the resetting of the imprinting pattern. In this case, progeny inheriting paternal microdeletions do not develop AS, but maternal transmis-

sion to offspring results in AS. These PWS and AS microdeletion results support the IC hypothesis, but a bipartite structure must be present since the minimally deleted regions responsible for PWS and AS are distinct.⁸⁷ An alternate mechanism for imprinting maintenance in this region relies on an enhancer-competition model between *cis*-linked genes;^{4,88} however, methylation analysis of the PWS/AS region reported by Schumacher et al⁸⁹ does not support this.

Imprinting in Brain and Behavior Development

The paternally expressed human *MEST* gene maps to 7q32, a region where maternal UPD is associated with intrauterine and postnatal growth retardation.^{21,90} Recently, a targeted deletion was introduced into the coding sequence of the mouse *Mest* gene to determine its function.⁹¹ When the deletion was paternally derived, *Mest* +/- mice were viable and fertile; however, they exhibited growth retardation and increased lethality. *Mest*-/+ animals (deletion maternally derived) showed none of these effects indicating that the phenotypic consequences of this mutation are detected only through paternal inheritance. Interestingly, Lefebvre et al⁹¹ found decreased reproductive fitness in the females that inherited the targeted disruption from their father. This effect was not based on the genotype of the progeny, but rather was due to an abnormal nurturing behavior of the mutant parturient females. Aberrant behavior of the mothers included failure to ingest the extraembryonic tissues (a normal behavior in most mammals), reduced rate of nest building, and pup neglecting. When the pups were fostered to wild-type females, no phenotypic differences between wild-type pups and *Mest*-/+ pups were apparent.

The results of this study demonstrate that the paternally expressed *Mest* is a positive regulator of embryonic growth, and is involved in the regulation of mammalian behavior associated with the rearing of offspring. These findings are consistent with the hypothesis that the imprinting of genes arises from the conflict of interest of the parental genomes in mammals,²⁸ and supports the importance of imprinted genes in brain development. Previous results using Pg and Ag mouse embryos suggested that both maternally and paternally derived genes contribute to the growth and function of specific brain regions in a complementary fashion.⁹² Keverne et al⁹³ found that Ag cells primarily contributed to hypothalamic composition, whereas Pg cells localized to the cortex, striatum, and hippocampus, but not to the hypothalamus. Brain growth was enhanced by Pg cells and retarded by Ag cells, further supporting the postulate that genomic imprinting is critically involved in mammalian brain development.

Evidence for imprinting effects in human diseases associated with mental abnormalities includes the aforementioned Prader-Willi and Angelman syndromes. There is now also evidence of cognitive imprinting effects in humans displaying normal intelligence. Skuse et al⁹⁴ recently reported that an imprinted X-linked locus is poten-

tially responsible for differences in cognitive function of females with Turner's syndrome. Although normal females (46,XX) inherit an X chromosome from both their mother and father, only one X chromosome is inactivated. Turner's syndrome is a sporadic disorder resulting when all or part of one X chromosome is deleted in females. These females display normal intelligence, but overall have a higher incidence of social difficulties.^{95,96} Turner syndrome women who inherit the X chromosome from their mother (45,Xm) generally exhibit more behavioral difficulties than those inheriting the X chromosome from their father (45,Xp). This finding provides the first evidence of genomic imprinting on the human X chromosome.⁹⁴ Based on cytogenetic analysis of these patients, partial deletions of the short arm of the paternally derived X chromosome were found. This suggests that the putative imprinted locus escapes X-inactivation and potentially lies in Xp11.23-Xqter. Interestingly, Miller and Willard⁹⁷ have recently identified a 5.5 megabase region on the human Xp11.21-p11.22 that contains eight expressed sequences which escape X inactivation. However, an imprinted gene(s) in this region is yet to be identified.

Parent-of-origin effects involved in other behavioral and brain disorders have also been reported. Included among these are bipolar affective disorder,⁹⁸⁻¹⁰⁰ schizophrenia,^{101,102} and autism.¹⁰³ However, the involvement of genomic imprinting in these examples remains to be elucidated. For an extensive summary of parent-of-origin effects in human disease, consult Morison and Reeve.¹⁰⁴

Imprinting in Human Cancer

There are numerous reports of tumors showing a bias in allelic loss. On a genome-wide scale, the complete hydatidiform mole and benign ovarian dermoid cyst arise from cells that are completely Ag or Pg in origin, respectively.^{105,106} In addition, numerous tumors are associated with the preferential loss of a particular parental chromosome, indicating the involvement of imprinted genes. Examples include neuroblastoma (maternal chromosome 1p36 and paternal chromosome 2),¹⁰⁷ acute myeloblastic leukemia (paternal chromosome 7),¹⁰⁸ Wilms' tumor (maternal chromosome 11p15.5),¹⁰⁹ rhabdomyosarcoma (maternal chromosome 11p15.5),¹¹⁰ and sporadic osteosarcoma (maternal chromosome 13).¹¹¹ A role for genomic imprinting has also been implicated in the development of familial glomus tumors based on inheritance patterns since tumor susceptibility is inherited paternally.¹¹²

Imprinted genes can be involved in carcinogenesis in several ways (Figure 3). Loss of heterozygosity or UPD at an imprinted region may result in the deletion of the only functional copy of a tumor suppressor gene. Alternatively, LOI or UPD of an imprinted gene that promoted cell growth may allow gene expression to be inappropriately increased. Finally, mutational inactivation of an IC might result in the aberrant expression of multiple imprinted oncogenes and/or tumor suppressor genes present in an imprinted chromosomal region.

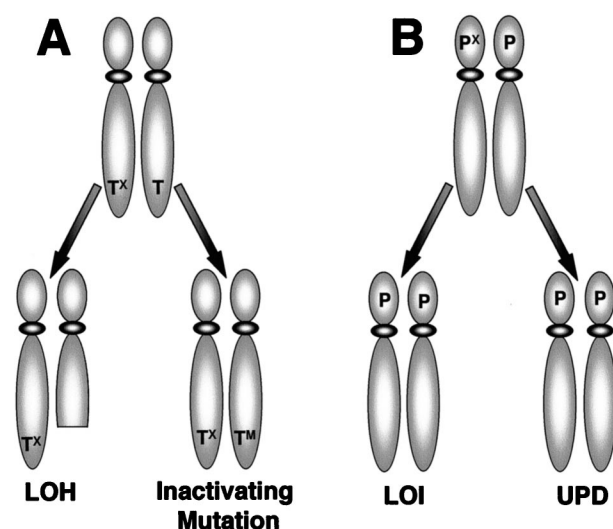


Figure 3. A: Only one allele of a tumor suppressor gene (T) is expressed because of genomic imprinting (T^X). Loss of heterozygosity (LOH) of the expressed allele or an inactivating mutation in the expressed allele (T^M) results in loss of tumor suppressor function. B: Only one allele of the proto-oncogene (P) is expressed because of genomic imprinting (P^X). Loss of imprinting (LOI) or uniparental disomy (UPD) results in biallelic expression of the proto-oncogene.

Aberrant genomic imprinting and its role in cancer are best exemplified by studies on Wilms' tumor, a childhood tumor that arises from metanephric blastemal cells. Direct genetic evidence linking tumorigenesis and aberrant imprinting was identified when 70% of Wilms' tumors were found to have biallelic *IGF2* expression.¹¹³⁻¹¹⁵ Inactivation of *H19* was also present in a number of these cases.¹¹⁵ The *H19* gene possesses a CpG island in its promoter that is normally methylated on the paternal allele and unmethylated on the maternal allele.^{44,45,115} An enhancer competition model for the reciprocal control of expression of the imprinted *IGF2* and *H19* genes has recently been proposed.^{116,117} Thus, LOI of the *IGF2* gene in Wilms' tumor could result from loss of *H19* expression.^{116,117} This scenario is supported by the finding that *H19* null transgenic mice show biallelic expression of *IGF2*.¹¹⁸ The coupling of biallelic *IGF2* gene expression with *H19* inactivation is even observed in phenotypically normal kidney tissue surrounding the Wilms' tumor. This suggests that the inactivation of *H19* and the biallelic expression of *IGF2* are linked, and occur early in development.¹¹⁹ Other human malignancies showing LOI at the *IGF2* locus are presented in Table 2. These results indicate deregulation of *IGF2* imprinting is mechanistically involved in the development of a variety of tumors.

Because imprinted genes are functionally haploid, an imprinted tumor suppressor gene would be predicted to increase cancer susceptibility since the inactivation of only one allele would eliminate tumor suppressor function. *WT1*,^{120,121} *p57^{KIP2}*,¹²²⁻¹²⁴ and *M6P/IGF2R*¹²⁵⁻¹²⁸ represent imprinted genes implicated in tumor suppression. *p57^{KIP2}*, mapped to 11p15.5, encodes for a cyclin-dependent kinase inhibitor that is maternally expressed. Epigenetic silencing of the expressed allele has been reported in some tumors and BWS patients.⁶³ Additionally, approximately 5% of BWS patients have *p57^{KIP2}*

Table 2. Aberrant Imprinting in Human Cancer

Tumor type	Gene	Reference
<i>Childhood Tumors</i>		
Wilms' tumor	<i>IGF2,H19,p57^{KIP2},M6P/IGF2R</i>	63, 113, 139, 162
Rhabdomyosarcoma	<i>IGF2</i>	203
Ewing's sarcoma	<i>IGF2</i>	204
Hepatoblastoma	<i>IGF2</i>	205, 206
<i>Adult Tumors</i>		
Bladder	<i>IGF2,H19,IPW</i>	207, 208
Breast	<i>IGF2</i>	209, 210
Cervical	<i>IGF2,H19</i>	211
Choriocarcinoma	<i>IGF2,H19</i>	212
Colorectal	<i>IGF2</i>	213
Esophageal	<i>H19</i>	214
Gastric adenocarcinoma	<i>IGF2</i>	215
Glioma	<i>IGF2</i>	216
Hepatocellular	<i>IGF2,H19</i>	217, 218
Leukemia-acute myeloid	<i>IGF2</i>	219
Leukemia-chronic myelogenous	<i>IGF2</i>	220
Lung	<i>IGF2,H19,p73</i>	221-223
Medulloblastoma	<i>IGF2,H19</i>	224
Mesothelioma	<i>IGF2</i>	225
Ovarian	<i>IGF2</i>	226
Prostate	<i>IGF2</i>	227
Renal cell carcinoma	<i>IGF2,p73</i>	148, 228
Testicular germ cell	<i>IGF2,H19</i>	229
Uterine	<i>IGF2</i>	230

mutations;⁶⁴ however, *p57^{KIP2}* mutations have not been identified in tumors. Thus, the putative tumor suppressor function of *p57^{KIP2}* remains to be clarified. Recently, *NOEY2 (ARHI)*, a novel *ras*-related, maternally imprinted gene at 1p31, was identified as a putative tumor suppressor gene in breast and ovarian carcinomas. In the majority of cases, the functional allele was lost.¹²⁹

Recent reports demonstrate that the *M6P/IGF2R* at 6q26 is inactivated in a variety of tumors at the earliest stage of transformation.¹²⁶⁻¹²⁸ The *M6P/IGF2R* plays an integral part in the intracellular sorting of lysosomal enzymes, the activation of the growth inhibitor transforming growth factor- β 1 (TGF- β 1), and the degradation of IGF2, but it is not directly involved in cell signaling.^{19,130} The *M6P/IGF2R* is mutated in 60% of dysplastic liver lesions and hepatocellular carcinomas of patients with or without hepatitis virus infection.^{125,126,128} The *M6P/IGF2R* is also mutated in 30% of breast tumors,¹²⁷ and the gene contains a polyG region that is a common mutational target in colon, gastric and endometrial tumors with mismatch repair deficiencies and microsatellite instability.^{128,131,132} Moreover, it has recently been reported that the *M6P/IGF2R* is mutated in human glioma samples that do not contain mutations in the transforming growth factor- β type II receptor (*TGFBRII*) or *Bax* genes.¹³³ In both breast^{127,134} and liver carcinogenesis,¹²⁸ the allelic inactivation of *M6P/IGF2R* occurs as an early event, during the initiation rather than the progression stage of transformation.

Although imprinting among individuals and mammalian species is generally conserved, the imprint status of *M6P/IGF2R* in humans and rodents is strikingly different. The *M6p/Igf2r* is imprinted in mice¹⁸ and rats,¹³⁵ but imprinting at this locus appears to be a polymorphic trait

in humans, with most individuals having biallelic expression.¹³⁶⁻¹³⁸ The existence of individuals with an imprinted *M6P/IGF2R* tumor suppressor suggests that they may have increased susceptibility to tumor development because of aberrant imprint control. This postulate is supported by Xu et al¹³⁹ who recently reported partial imprinting of *M6P/IGF2R* in 50% of Wilms' tumor patients.

The precise molecular mechanism for genomic imprinting of *M6P/IGF2R* is not completely defined. Methylation of a CpG rich region in intron 2 (Region 2) of the expressed maternal allele has been shown to carry the imprint signal for this gene in mice.^{46,140} Birger et al¹⁴¹ have identified a 113-bp sequence, in region 2 of the mouse *M6p/Igf2r* gene, that serves as a methylation imprinting box responsible for the establishment of differential methylation. Furthermore, this region appears to function as the promoter of an antisense transcript that originates only from the repressed paternal allele. This indicates that a form of expression competition regulates imprinting of the *M6p/Igf2r* gene in mice.¹⁴⁰ Region 2 of the human *M6P/IGF2R* also contains parent-of-origin methylation, but gene expression is biallelic.^{142,143} Consequently, humans and mice appear to possess an altered ability to read the *M6P/IGF2R* imprint marks.

Functional polymorphic imprinting has also been observed for human genes encoding *IGF2*,¹⁴⁴ *WT1*,¹²⁰ and the human 5-HT2A receptor gene *HTR2A*.¹⁴⁵ Recently, the mouse *Kvlqt1* gene has been shown to undergo developmental relaxation of imprinting in a strain-dependent fashion.¹⁴⁶ Whether polymorphic genomic imprinting occurs in other genes, and functions in determining individual and/or species differences in susceptibility to diseases remains to be determined.

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